SUPPLEMENTARY FIGURES AND TABLES

Progression-free survival

A

	Events / Patients		HR (95% CI)		HR & CI		Interaction test
	Cilengitide/TMZ	TMZ alone			(Cilengitide/TMZ	TMZ alone)	
αvβ3, tumor cells							
≤median	72 / 111	72 / 103	0.81	(0.59 ; 1.13)			p=0.266 (df=1)
>median	29 / 41	29 / 39	1.15	(0.69 ; 1.93)			
	N missing = 251						
αvβ3, endothelial cells							
≤median	49 / 71	50 / 70	0.77	(0.52 ; 1.14)			p=0.324 (df=1)
>median	52 / 81	51 / 72	1.02	(0.69 ; 1.50)			
	N missing = 251						
αvβ5, tumor cells							
≤median	45 / 69	49 / 75	0.93	(0.62 ; 1.39)			p=0.692 (df=1)
>median	56 / 84	51 / 66	0.83	(0.57 ; 1.21)			
	N missing = 251						
αvβ5, endothelial cells							
≤median	50 / 76	48 / 69	0.75	(0.50 ; 1.11)			p=0.248 (df=1)
>median	49 / 75	52 / 72	1.04	(0.70 ; 1.53)			
	N missing = 253						
αvβ8, tumor cells							
≤median	49 / 74	43 / 65	0.98	(0.65 ; 1.47)			p=0.700 (df=1)
>median	48 / 70	56 / 74	0.88	(0.60 ; 1.29)			
	N missing = 262						
αvβ8, endothelial cells							
≤median	87 / 129	94 / 129	0.87	(0.65 ; 1.17)			p=0.198 (df=1)
>median	10 / 15	5 / 10	1.79	(0.61 ; 5.25)			
	N missing = 262						
pSMAD2, tumor cells							
≤median	44 / 69	46 / 67	0.88	(0.58 ; 1.33)			p=0.903 (df=1)
>median	50 / 73	53 / 72	0.91	(0.62 ; 1.34)			
	N missing = 264						
pSMAD2, endothelial cells							
≤median	40 / 67	47 / 72	0.89	(0.59 ; 1.36)			p=0.987 (df=1)
>median	54 / 75	52 / 67	0.89	(0.61 ; 1.30)			
	N missing = 264						
Total	193 / 272	194 / 273	0.95	(0.78 ; 1.16)			
	(71 %)	(71.1 %)					

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0.25        0.5        1.0       2.0       4.0
      Cilengitide/TMZ          TMZ alone
          better                 better
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Unadjusted treatment effect: p= 0.590

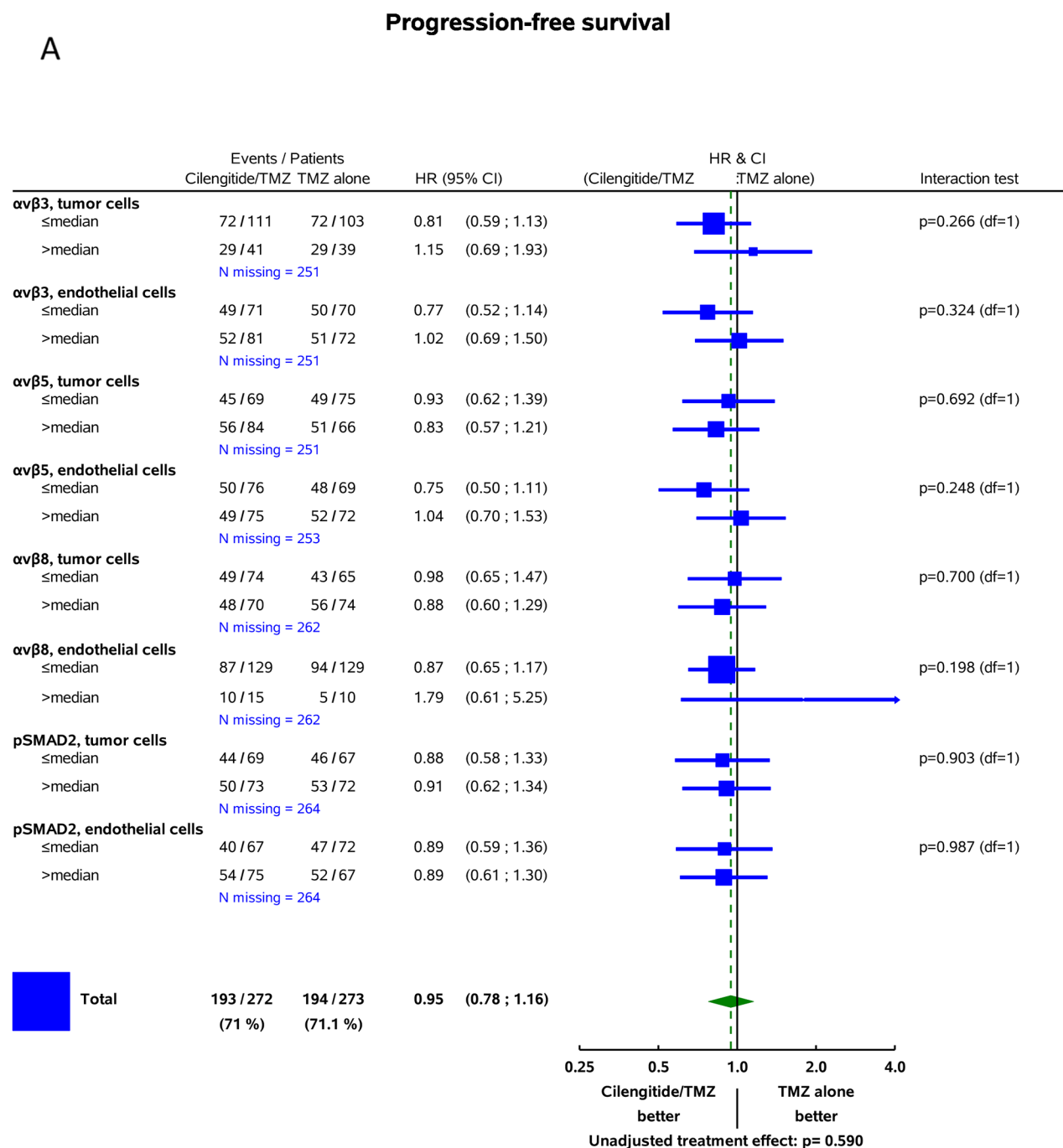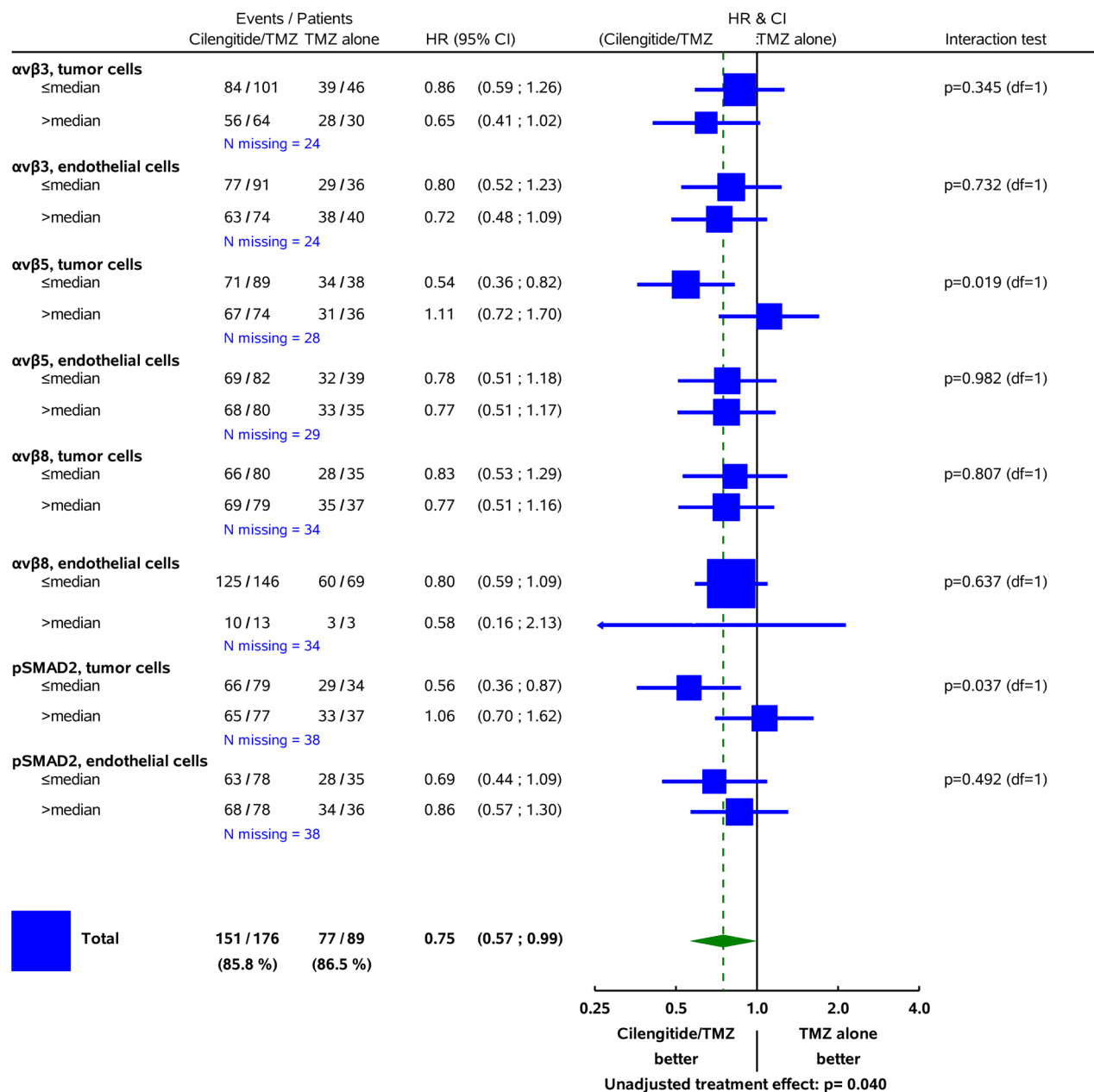**Supplementary Figure 1: Forest plots: predictive value of biomarkers for the efficacy of cilengitide for investigator-assessed PFS. A.** CENTRIC (*continued*)

Progression-free survival

B

	Events / Patients		HR (95% CI)		Interaction test
	Cilengitide/TMZ	TMZ alone			
αvβ3, tumor cells					
≤median	84 / 101	39 / 46	0.86	(0.59 ; 1.26)	p=0.345 (df=1)
>median	56 / 64	28 / 30	0.65	(0.41 ; 1.02)	
	N missing = 24				
αvβ3, endothelial cells					
≤median	77 / 91	29 / 36	0.80	(0.52 ; 1.23)	p=0.732 (df=1)
>median	63 / 74	38 / 40	0.72	(0.48 ; 1.09)	
	N missing = 24				
αvβ5, tumor cells					
≤median	71 / 89	34 / 38	0.54	(0.36 ; 0.82)	p=0.019 (df=1)
>median	67 / 74	31 / 36	1.11	(0.72 ; 1.70)	
	N missing = 28				
αvβ5, endothelial cells					
≤median	69 / 82	32 / 39	0.78	(0.51 ; 1.18)	p=0.982 (df=1)
>median	68 / 80	33 / 35	0.77	(0.51 ; 1.17)	
	N missing = 29				
αvβ8, tumor cells					
≤median	66 / 80	28 / 35	0.83	(0.53 ; 1.29)	p=0.807 (df=1)
>median	69 / 79	35 / 37	0.77	(0.51 ; 1.16)	
	N missing = 34				
αvβ8, endothelial cells					
≤median	125 / 146	60 / 69	0.80	(0.59 ; 1.09)	p=0.637 (df=1)
>median	10 / 13	3 / 3	0.58	(0.16 ; 2.13)	
	N missing = 34				
pSMAD2, tumor cells					
≤median	66 / 79	29 / 34	0.56	(0.36 ; 0.87)	p=0.037 (df=1)
>median	65 / 77	33 / 37	1.06	(0.70 ; 1.62)	
	N missing = 38				
pSMAD2, endothelial cells					
≤median	63 / 78	28 / 35	0.69	(0.44 ; 1.09)	p=0.492 (df=1)
>median	68 / 78	34 / 36	0.86	(0.57 ; 1.30)	
	N missing = 38				
Total	151 / 176	77 / 89	0.75	(0.57 ; 0.99)	
	(85.8 %)	(86.5 %)			

HR & CI
(Cilengitide/TMZ   TMZ alone)

0.25   0.5   1.0   2.0   4.0

Cilengitide/TMZ better   **TMZ alone better**

Unadjusted treatment effect: p= 0.040

Supplementary Figure 1: (*continued*) **Forest plots: predictive value of biomarkers for the efficacy of cilengitide for investigator-assessed PFS. B.** CORE. On the left-hand, the integrin subgroups with numbers of events/sample size by treatment arm, number of missing data, and hazard ratios (HR) with 95% confidence intervals are shown. The vertical line represents the absence of differential effects between the two treatments, i.e., if for an integrin subgroup, the 95% confidence intervals overlap with this line, it indicates that treatment effects are not different. The square represents the Cilengitide/TMZ hazard ratio in the integrin subgroup. The area of each square is proportional to the number of events. The diamond indicates a differential effect of treatment in the whole cohort. Diamond overlapping the vertical lines indicates in-significantly different treatment effects at 5% significance. On the right-hand, interaction tests are presented. They assess the significance of a differential treatment effect between two integrin subgroups, i.e., tests have one degree of freedom (df=1).

Supplementary Table 1: Outcome in the CENTRIC and CORE clinical trials: patients without or with incomplete biomarker data compared to patients in the biomarker cohort

	Progression-free survival				Overall survival			
	Patients/ events	Median (95% CI)	Hazard ratio	p value	Patients/ events	Median (95% CI)	Hazard ratio	p value
CENTRIC								
No or incomplete biomarker data	271/199	13.0 (10.1, 15.1)	1.0	0.57	271/148	27.1 (24.8, 33.7)	1.0	0.45
Biomarker cohort	274/188	12.1 (10.4, 13.6)	1.1 (0.9, 1.3)		274/134	25.4 (23.3, 30.9)	1.1 (0.9, 1.4)	
CORE								
No or incomplete biomarker data	41/37	6.0 (4.0, 9.9)	1.0	0.86	41/32	16.6 (12.0, 20.5)	1.0	0.46
Biomarker cohort	224/191	6.3 (5.9, 7.7)	1.0 (0.7, 1.5)		224/166	14.1 (12.9, 15.4)	1.2 (0.8, 1.7)	

Supplementary Table 2: Correlation of biomarker staining results

(See Supplementary File 1)

Supplementary Table 3: Association of integrin and pSMAD2 levels with PFS

(See Supplementary File 2)

Supplementary Table 4: Association of integrin and pSMAD2 levels with OS

(See Supplementary File 3)